PTO 2001-2694

CY=EU DATE=19980422 KIND=A1
PN=837331

AN AUTOMATIC IMMUNOLOGICAL DOSAGE DEVICE
[Appareil Automatique De Dosage Immunologique]

Thierry Gicquel, et al.

UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. June 2001

Translated by: Diplomatic Language Services, Inc.

PUBLICATION COUNTRY	(19):	EU
DOCUMENT NUMBER	(11):	0837331
DOCUMENT KIND	(12):	A1
	(13):	
PUBLICATION DATE	(43):	19980422
PUBLICATION DATE	(45):	
APPLICATION NUMBER	(21):	97402351.7
APPLICATION DATE	(22):	19971007
ADDITION TO	(61):	
INTERNATIONAL CLASSIFICATION	(51):	G01N 35/02
DOMESTIC CLASSIFICATION	(52):	
PRIORITY COUNTRY	(33):	
PRIORITY NUMBER	(31):	
PRIORITY DATE	(32):	
INVENTOR	(72):	GICQUEL, THIERRY; LENTWOJT, EDOUARD
APPLICANT	(71):	LABORATOIRES MERCK-CLEVENOT
TITLE	(54):	AN AUTOMATIC IMMUNOLOGICAL DOSAGE DEVICE
FOREIGN TITLE	[54A]:	APPAREIL AUTOMATIQUE DE DOSAGE IMMUNOLOGIQUE

Description /1*

The invention concerns a dosage device for different immunological substances in biological samples that allows for the automation of ELISA, RIA, FIA, LIA, FPLIA, CLIA, etc. dosage methods.

Devices of this type are already described in International Patents WO-9107662 and WO-9614582 which may be referred to for a description of the doses achieved. These known devices mainly consist of the means of support, guidance, and step-by-step movement of reagent cups on a path that has a number of predetermined positions, a supporting rotating plate with specimens that are to be analyzed, a rotating plate with reagent supports, a means of taking determined quantities of specimens and reagents, and the injection of these takings in the reagent cups, means for cleaning the cups, means for optical reading of the dosage results, and a data processing system that allows for preprogrammed cyclical analysis corresponding to the mono- or bi-reagent type, these known devices having a functional rate on the order of 120 doses per hour for the first among them, and 360 doses per hour for the second.

The device described in International Patent WO-9614582 moreover distinguishes itself in that it is made to function with reagent modules that are molded from plastic material and consists of several aligned reagent cups that are interdependent with one another, these reagent modules being mass produced at low cost, which allows them to be discarded after a single use. Further, these reagent modules may be

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* Numbers in the margin indicate pagination in the foreign text.

stacked, which facilitates packaging as well as stacking within the automatic supply means of the device.

This known device is also characterized by the means through which the reagent modules are guided and moved along the open U-shaped loop track, the ends of which are respectively designed with the automatic supply means of the reagent modules and the automatic ejection means of the reagent modules.

This device has as an advantage the ability to function at a higher rate (360 doses per hour), but it is more cumbersome and more expensive than that described in International Patent WO-9107662.

The present invention has as its subject an automatic immunological dosage device that combines the advantages of these two known devices while avoiding their inconveniences.

To this end, it proposes a device of the previously-described type consisting of the means of support, guidance, and step-by-step movement of groups of reagent cups on a path that has a number of predetermined positions, a means of support for the specimens that are to be analyzed, a means of support for the reagents, a means of taking predetermined quantities of specimens and reagents, and the injection of these takings in the reagent cups, as well as means for cleaning the cups, means for reading the results, and means for supplying all of the reagent cups and ejecting all of the used cups, characterized such that the path of the reagent cups is rectangular and consists of two large sides defined by the parallel rectilinear support and guidance rails of all of the cups, and two small sides defined by means of right angle movement of the cups on three positions consisting of two end positions on the large sides of

the shape and an intermediate position that consists of the ejection position of a group of used cups and the supply position of a new group of cups.

The means of moving the groups of cups in accordance with the invention are simpler and more reliable than those used in the prior art, particularly due to the fact that the paths of the groups of cups are rectilinear and have no curved parts, the transfer of groups of cups in the three positions of the design on the small sides of their rectangular shape allowing for simplification of how the groups of new cups are led about and of the automatic ejection of the groups of used cups.

In accordance with another characteristic of the invention, the means of right angle movement of the groups of cups occur on the large sides of the path at intervals that fall between two movement steps of the groups of cups.

In a preferred implementation mode of the invention, the means for moving the groups of cups on the large sides of the shape consist of a notched belt whose ribs grip the plates that are longitudinal to the groups of cups and which are guided along the exterior rail of each large side of the shape, while the means of right angle movement consist of the means of gripping the two groups of cups and the means of raising [them], the means of right angle movement and lowering of the latching means, these latter consisting of a right angle vertical plate that is movable under the groups of cups and capable of being inserted between two cups of a group in order to raise it from the support rails and move it to a position in the other.

The means for supplying the device with groups of reagent cups consist of storing magazines of stacked groups of nested cups, a cart for capturing and moving a group of cups horizontally, a guide under the open interior ends of the magazines which can be moved to the /2
previously described intermediary position, which is the supply and ejection position, the magazines being equipped with pivoting arms that hold the group of cups that are below each storage pile and which are moved away by the cart when it passes under the pile in order to release the lower group of cups and let it fall into a housing assembled in the cart when this housing is not already occupied by another group of reagent cups.

The means for ejecting the groups of used cups consist of a slide or an open chute formed along the previously described lower intermediate position such that the input of a group of new cups into this intermediary position by the means of supply causes the group of used cups that occupy this intermediate position to be moved to the slide or the chute's opening.

Generally, the device in accordance with the invention benefits from all of the advantages linked to the use of modular groups of reagent cups described in International Patent WO-9614582, all while simplifying the means of movement of these groups of cups and reducing their disadvantages and maintaining the cost advantages of the device described in International Patent WO-9107662, all while simplifying and improving the use of this latter.

The invention is better understood and other characteristics, details, and advantages are made clear in the writing and description

that follow, which are offered by way of example with reference to the attached diagrams, in which:

- figure 1 is an overhead schematic of the device in accordance with the invention;
- figure 2 is a schematic of a group of reagent cups;
- figure 3 is a partial lower schematic of the means of support and the drive assembly of a group of cups:
- figures 4 and 5 are elevated views and a cutaway that schematically represent the means of positioning a group of cups;
- figure 6 is a vertical cutaway schematic of the means of supply for groups of reagent cups;
- figures 7 and 8 are partial overhead schematics that illustrate how these supply means function;
- figure 9 is a cutaway view of the means of right angle movement of groups of cups;
- figures 10 and 11 are, respectively, vertical and overhead cutaway schema of these means of right angle movement;
- figures 12, 13, 14, and 15 schematically illustrate the operation of the means of movement of the cups in the device in accordance with the invention.

The device in accordance with the invention, where the general structure is represented in figure 1, consists of a chassis (10) on which are mounted a turning support plate (12) with samples to be analyzed, a turning support plate (14) with reagent doses, means of removal for a specific quantity of sample and a specific quantity of reagent, respectively (16, 18), and a means of depositing these sampled

quantities in a reagent dish, these means being of the same type as those described in International Patent WO-9614582, whose contents are referenced here.

The reagents that are used are of the magnetic ball type, and the device in accordance with the invention consists of means (20) for cleaning or rinsing these magnetic balls, which are of the same type as those already described in the previously cited International Patents, and which consist of vertically placed aspiration and liquid injection needles, and permanent magnets placed on each side of the means of movement of the reagent cups in order to draw the magnetic reagent balls by magnetic attraction and affix them temporarily on the walls of the reaction cups. The means (20) also consist of a needle for depositing a substrate in the reagent cups, which is placed immediately downstream from the liquid injection and aspiration needles for cleaning.

The means (22) for optically reading the results of the dosage, which are of the same type as described in the aforementioned International Patents, are arranged on the chassis (10) near the means (20) of injection and cleaning.

The device in accordance with the invention again consists of the means of moving groups of reagent cups along a rectangular path with an end to which are designed means (24) of automatic supply and positioning of groups of reagent cups and means of ejecting these cups, these means being described in greater detail in what follows.

The groups of reagent cups and their means of movement and positioning are represented in figures 2 to 5.

The groups (26) of reagent cups (figure 2) are made with a

transparent molded plastic material, and each consists of eight reagent cups (28) aligned on the longitudinal axis of the group (26) and joined to one another, each group consisting of two upper longitudinal edges (30) that are L-shaped and extend above the open ends of the cups (28).

Each longitudinal edge (30) consists at the level of each dish (28) of a truncated hole (32) that precisely positions the group (26) in specific positions of the device in accordance with the invention, and /3 the exterior lateral faces of the edges (30) each consist of vertical ribs (34) that articulate with the groups' drive assembly (26).

As described in International Patent WO-9614582, the cups (28) are rectangular lengths of tube closed at the lower end and wider at their upper end, which allows the groups (26) to be stacked vertically by partially nesting then in each other, the lower parts of the cups (28) of a group (26) inserting into the upper wide ends of the cups (28) of a lower reagent dish assembly. This nesting is facilitated by the fact that the interior faces of the longitudinal edges (30) differ slightly from one another along the top from the open upper ends of the cups (28).

Vertical ribs (36) are formed on the sides of the wide upper ends of the cups (28) and extend around the base for a short distance, the lower ends of these ribs (36) being meant to support the edges (30) of a lower group (26) on these upper faces in a vertical stack of groups of reagent cups.

Along the longer sides of their rectangular path in the device, the groups (26) of cups stand by their longitudinal edges (30) on rails or parallel rectilinear shapes (38) between which the cups (28) are placed.

A notched belt (40) is guided on the exterior rail (38) of each large side of the form described previously and passes over four pulleys, where two of the pulleys are juxtaposed at right angles to position 42 of figure 1, and where the other two are juxtaposed at right angles to the end of the supply means (24), one of these pulleys being the motor for the step-by-step movement of the groups of cups (26) at equal distances between the reagent cups (28).

The belt notches (40) grab the longitudinal edges (30) of groups of cups (26) that are moved by sliding on the rails (38) by means of vertical ribs (34) without particular effort due to their minimal weight and the low friction between the material of the groups (26) and the rails (38).

Means for precisely positioning the groups (26) are designed on the path of the device, to places where the products must be placed in the reagent cups or evacuated from these cups.

These means of positioning are laid out at the level of the means (20) of cleaning. They consist of horizontal plates (43) that can be placed vertically and which on their lower side consist of vertical rows (44) designed to articulate with the holes (32) of the vertical edges of the groups of cups (26) in order to position them longitudinally and at right angles in a precise way in comparison with the injection or aspiration needles (46), which thus can be lowered in the reagent cups (28) close to the base of these cups without risking coming up against a solid wall.

The structure of the means (24) of supply of new groups of cups and their method of functioning are illustrated in figures 6 to 8.

These means (24) consist of three magazines (50) containing vertical stacks of groups of cups (26) nested in one another, these magazines (50) being vertical pipes with an open upper end in order to allow for a stack of groups of cups (26) to be loaded, and an open lower end in order to lay out a group of cups (26) on a transport cart (52) of this group up to a supply position designed at one end of the rectangular form described previously.

Each magazine (50) is equipped with two vertical arms (54) that are mounted such that they are able to pivot on horizontal axes (56) and have perpendicular cogs (58) at their lower ends that are meant to engage under the lower ends of the magazines (50) in order to hold the lower group of a vertical stack (26) contained in this magazine, this lower group (26) being led by these vertical edges (30) that rest on the ends of the cogs (58) of the arms (54).

The arms (54) also consist of a heel (60) that is meant to work with a roller (62) of the cart (52) such that to the passage of the rollers (62) on the heel (60), the arms (54) separate around the exterior in order to allow the lower group (26) to slip out of a stack contained in the magazine (50). Return springs (not shown) allow the arms (54) to maintain a basically vertical position against the magazine (50) in order to keep the group stacked (26) when the heels (60) are freed by the rollers (62).

The cart (52) is moved horizontally under the magazines (50) by two threaded rods (64) placed in rotation by an electric motor and screwed into fixed screws in the cart (52).

Two rails (66) extend parallel to the threaded rods (64) in

cavities formed in the cart (52) in order to support these longitudinal edges (30) of the group (26) of reagent cups that are released from a magazine stack (50) and which fall by gravity inside a housing defined in the cart (52) by two longitudinal arms (68) (figures 7 and 8), the fore and aft ends of this housing being open in such a way that the cart (52) may be moved under the magazines (50) without harming the lower parts of the stacks of groups (26) of reagent cups contained in the magazines (50) (figure 6).

The means (24) of supply for the groups (26) of cups function as follows:

the cart (52) starts from its extreme forward position (the supply position of the groups of cups in the rectangular path) and starts to move backwards toward the first magazine (50), which contains a stack of groups (26) where the lower group (26) is represented by dotted lines /4 in figure 7. As the cart (52) moves backwards in the direction indicated by the arrow (70), the rollers (62) come up against the heels (60) of the arms (54) of the first magazine (50) (the upper part of figure 7) and begin to spread them outward (the lower part of figure 7). When the arms (54) are completely spread (figure 8), they release the lower group (26) of the stack contained in the magazine (50), which lowers to the bottom by gravity and falls in the housing designed in the cart (52). The cart (52) follow[s] its movement to the back in the direction indicated by the arrow (70), [and] these rollers (62) free the arms (54) of the first magazine (50), which are similar to one another with respect to their return springs, their cogs (58) that come to be engaged under the longitudinal edges (30) of the lower group (26) of the reagent

cups.

The speed of the cart (52) and the height of the chute of a group (26) are defined such that the passage of the rollers (62) on the heels (60) of the arms (54) releases a single group (26) of cups and prevents two groups (26) of cups from entering into the cart (52).

The cart (52) continues with its backward movement in the direction indicated by the arrow (70) in order to pass below the other magazines (50) where it spreads the arms (54) by the rollers (62), in order to release the lower group (26) of reagent cups in each continual stack in these magazines (50). However, the groups (26) thus released cannot fall into the housing designed to this end in the cart (52) already occupied by a group (26) of reagent cups, such that when they are released by the rollers (62), the arms (54) come to articulate with their cogs (58) under the edges of the lower group of a stack by slightly raising this latter.

When the cart (52) is passed under the last magazine (50), it is led to the front, pushes to pass through the arms (54) of each magazine, but without capturing a group (26) of reagent cups, and returns to the supply position situated before the first magazine (50).

The support rails (66) of the group (26) are interrupted right before this supply position, such that the group (26) of cups led by the cart in this position falls by gravity to a lower level where it slips from the arms (68) of the cart, which allows it to be led backward in order to capture a new group (26) of reagent groups.

It is understood from the preceding that the cart (52) takes the groups (26) of reagent dishes one after another from the first magazine

(50), then those that are in the second magazine (50) when the first magazine is empty, then those that are in the third magazine (50) when the first two are empty, the empty magazines being able to be refilled again at any time without it being necessary to interrupt the operation of the dosage device.

Refer to figures 9 to 11 now, which refer to the means of right angle movement of the groups of cups to the longitudinal ends of their rectangular path in the dosage device.

The rails (38) are extended at the ends of this form by sections (72) that define two end positions P1 and P3, where the groups of cups (26) are supported half by the rails (38) and half by the sections (72), and an intermediary position P2 that is between end positions P1 and P3 (figure 9).

The means for moving the groups of cups (26) in positions P1, P2, and P3 consist of a right angle vertical plate (74) arranged in the interval between the rails (38) and the sections (72) and led vertically in a cart (76) that itself is guided by alternating movement on the horizontal right angle rods (78) carried by the chassis (10), plate (74) and cart (76) being driven by an offset motor system.

This system consists of an electric motor (80) on the output tree to which is mounted a mobile vertical disc (82) that rotates around its own axis (84) and has an offset roller (86) which is received in a horizontal aperture (88) of the vertical plate (74) and which is mobile along the edge of a curved aperture (90) that is formed in a vertical wall (92) of the cart (76).

The curved aperture (90), which is roughly lemon-shaped, consists

of two opposed arcs (94) that are parallel to the edge of the disc (82) and which correspond to the form of the exterior periphery of the roller (86) driven by the disk (82), and two vertical abutments (96) to the upper and lower ends of the arcs (94).

These vertical abutments (96) allow for the movement of the cart (76) horizontally from left to right and right to left as in figure 9, when the disk (82) is rotating in the direction indicated by the arrow. When the roller (86) is in the position shown, as support on the lower vertical abutment (96), it moves the cart (76) to the right in figure 9 on chassis 10. During this movement, the vertical plate (74) is moved vertically a small distance.

The roller (86) slips from the vertical abutment (96) when the cart (76) is placed on the chassis (10) and thus starts to roll on the curved part (94) of the aperture (90), which has the effect of moving the plate (74) vertically without moving the cart (76). Then, the roller (86) comes to be supported on the lower vertical abutment (96) with the effect of moving the cart (76) to the left in figure 9 until it is applied to the chassis (10). The roller (86) then comes to be supported on the upper vertical abutment (96) and rolls on the inclined part (94) of the aperture (90), which has the effect of moving the vertical plate (74) along the base and leading it to the position represented in figure 9.

Thus, when the disk (82) and the roller (86) turn 360° around the /5
axis (84), the plate (74) is moved along a rectangular or square path, which is shown by arrows (98) in figure 9.

The upper edge (100) of the vertical plate (74) consists of three

teeth that are set at a distance equal to the interval between the rails (38) or the sections (72), and which are meant to engage under the lateral edges (30) of the groups of plates resting on the rails (38) and the sections (72) in order to lift them and release them from these rails and sections, such that the upper edge (100) of the plate (74) lies between the two middle cups (28) of each group (26) (figure 10).

When the vertical plate (74) is moved in accordance with the path noted by the arrows (98) in figure 9, it raises the two groups of cups (26) that are in positions P3 and P2 vertically, disengaging them from the rails and sections (38 an 72), leading them to positions P2 and P1, then relowering them vertically in order to deposit the groups (26) on the rails and sections (38 and 72).

The groups of cups (26) carried by the plate (74) are in a relatively stable position due to the fact that their edges (30) rest on the teeth (102) of this plate and that the upper edge (100) of this is articulated between the two middle cups (28) of each group (26).

The groups (26) are thus moved at right angles two at a time at the longitudinal ends of their rectangular path on the three positions P3, P3, P2, and P1 by the vertical plate (74) and its drive mechanism, which is activated between two steps before the groups (26) along the long sides of their rectangular path.

The intermediary position (P2) designed on the side of the means (24) of supply consists at the same time of a supply position for new groups of cups and an ejection position for used cups.

As is shown in figure 12, when a group (26) of new cups is led by the cart (52) in the supply position P2, it ejects the group (26) from

this position that is found there, which falls into an opening or on a slide chute (not shown) leading to a sink or trash can.

When a new group (26) of reagent cups replaces the group of used cups in position P2, the means of right angle movement designed at this end of the rectangular path move the groups of cups (26) which are found in positions P2 and P3, respectively, into positions P1 and P2, while at the other end of the device, the corresponding means of movement at right angles move the groups of cups in positions P1 and P2 that are found in positions P2 and P3.

The groups (26) are moved step-by-step along the longer sides of the rectangular path as shown in figure 14 until groups (26) of reagent cups again occupy the P3 positions, as shown in figure 15. The means of right angle movement of these groups are thus activated in order to transfer the groups of reagent cups in positions P1 and P2 which are found in positions P2 and P3, respectively.

In this device, a group (26) of reagent cups led to the supply position P2 must carry out the complete rectangular path twice for a single reagent dose, and three times for a double reagent dose, before being ejected as shown in figure 12.

The device in accordance with the invention can, in the same conditions described in International Patent WO-9614582, function at a rate of 120 doses per hour completely automatically.

Claims

1. An automatic device for immunological dosing consisting of the means of support, guidance, and step-by-step movement (26) of the reagent cups on a path consisting of a number of predetermined

positions, the means (12) of support for the samples to be analyzed, the means (14) of support of the reagents, the means of support (16, 18) of predetermined sample, reagent, and injection quantities in the reagent cups, as well as the means (20) of washing the cups, the means (22) of reading the results, and the means (24) of supply of the groups of reagent cups and the ejection of groups of used cups such that the path of the groups (26) of reagent cups is rectangular and consists of two large sides defined by parallel rectilinear support and guide rails (38) of the groups of cups (26) and two small sides defined by the means (74) of right angle displacement of the groups of cups (26) on three positions, P1, P2, and P3, consisting of two end positions P1, P3 on the large sides of the aforementioned path and an intermediary position P2 that constitutes the ejection position of a group of used cups, and the supply position of a new group of cups.

2. A device in accordance with claim 1 characterized such that the means of right angle movement move the groups of cups (26) two at a time at the three aforementioned positions, a group of cups being moved to an end position P3 from the intermediary position P2, and the other group of cups being moved to the intermediary P2 position from the other end position P1.

3. A device in accordance with claim 1 or 2 characterized such that /6 the means of right angle movement of the groups of cups (26) are activated at the intervals between two positioning steps of the groups of cups (26) on the large sides of the aforementioned path.

4. A device in accordance with claim 2 or 3 characterized such that

the means of right angle movement consist of the means (74) for gripping two groups of cups (26) and the means of lifting, right angle movement, and lowering of the means for gripping.

5. A device in accordance with claim 4 characterized such that the means for gripping consists of a vertical right angle plate (74) that may be moved under the groups of reagent cups in order to lift them by placing between two cups of each group.

6. A device in accordance with claim 5 characterized such that the right angle plate (74) is guided by moving it vertically in a cart (76) that is movable along a small side of the rectangular path of the groups of cups by means of a motor consisting of a rotating disk (82) with an offset roller (86) in a horizontal aperture (88) of the vertical plate (74) and in a curved aperture (90) of a cart wall (76).

7. A device in accordance with one of the preceding claims characterized such that the means (24) of supply of the groups of new cups consist of storage magazines (50) of stacks of cups that are nested in one another, a cart (52) for capturing and horizontal movement of a group of cups (26), guided under the lower open ends of the magazines (50) and movable up to the aforementioned intermediary position P2 forming a supply position and an ejection position, the magazines (50) being equipped with pivoting arms (54) that hold the group of cups (26) below each storage stack and which are opened by the cart (52) by its passage under the stack in order to release the lower group of cups of this stack and allow it to fall by gravity in a housing assembled in the cart (52) when this

housing is not occupied by another group (26) of reagent cups.

8. A device in accordance with claim 7 characterized such that the storage magazines (50) are aligned with said intermediary P2 supply and ejection position.

9. A device in accordance with one of the preceding claims characterized such that the means of ejecting the groups (26) of used cups consist of a slide or an open chute formed in the alignment of the aforementioned P2 intermediary position, such that the input of a group (26) of new cups in this intermediary position P2 by the means of supply (24) causes the group of used cups to be pushed to the slide or opening of the chute that occupies this intermediary position P2.

10. A device in accordance with one of the preceding claims characterized such that the means of moving groups (26) of cups on the large sides of the aforementioned path consist of a ribbed belt (40) that with the ribs (34) grips the longitudinal edges (30) of the groups of cups (26), this belt (40) being guided along the exterior rail of each large side of the aforementioned path.

11. A device in accordance with one of the preceding claims characterized such that the groups (26) of cups consist of longitudinal edges (30) that rest on the rails (38) that define the large sides of the aforementioned path, these edges on both sides consisting of holes (32) meant to receive mobile cogs (44) for positioning that are arranged at the aforementioned level of the means (20) of cleaning.

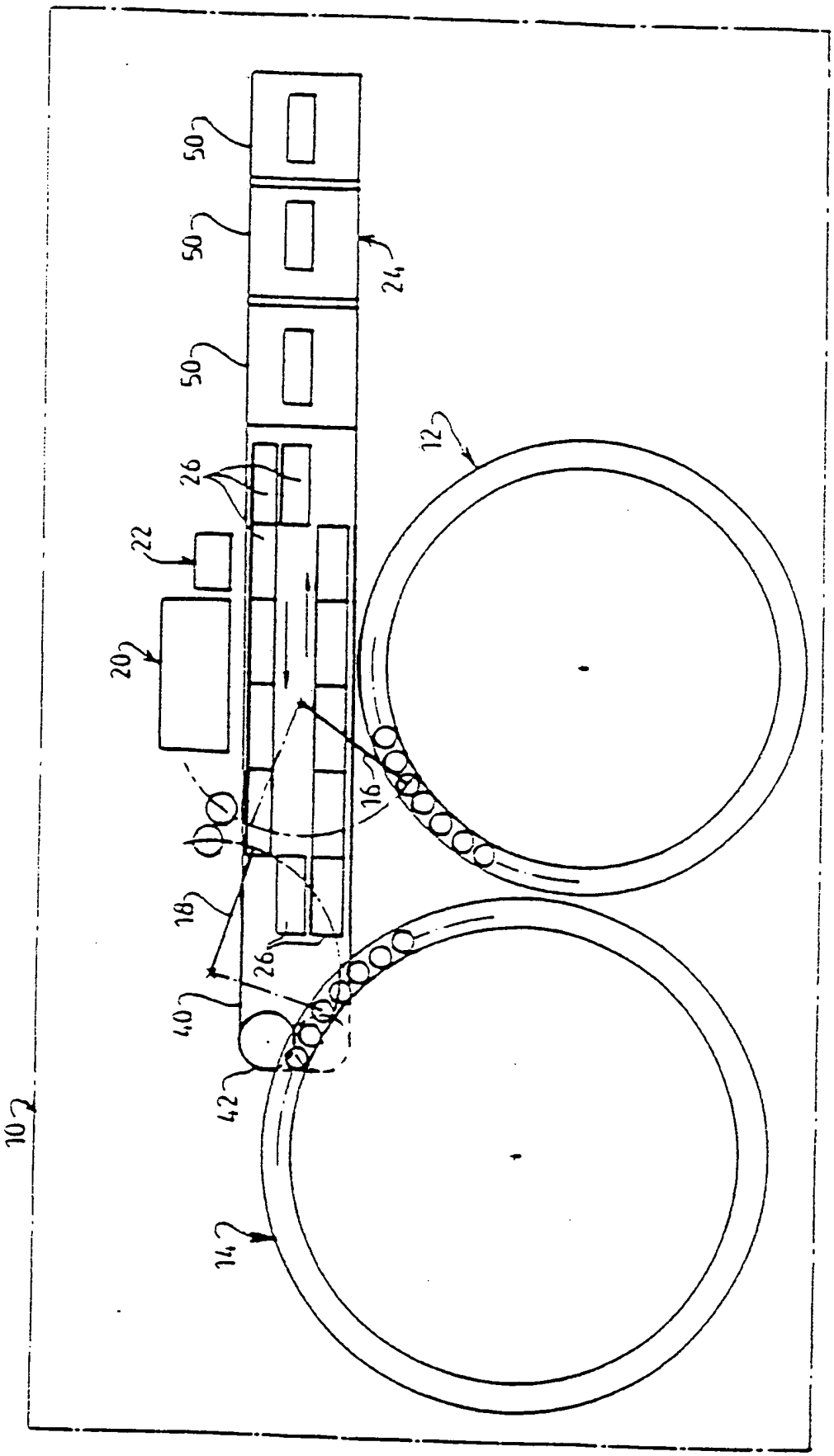

FIG.1

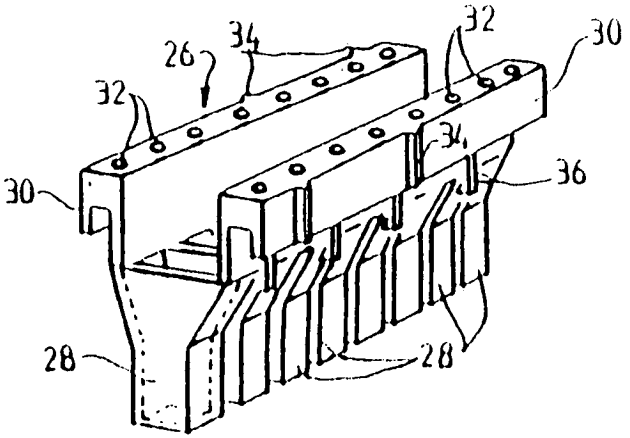

FIG. 2

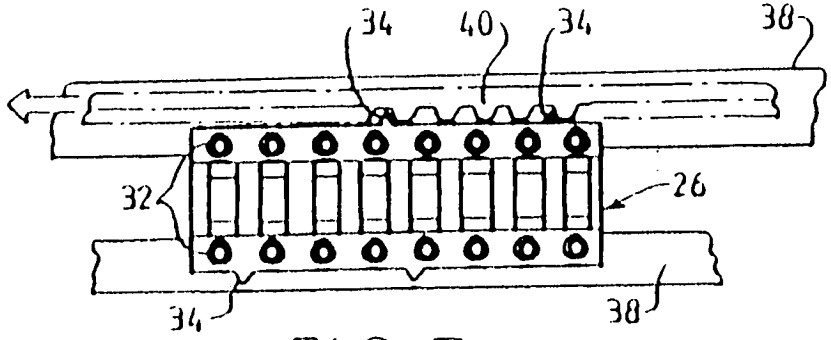

FIG. 3

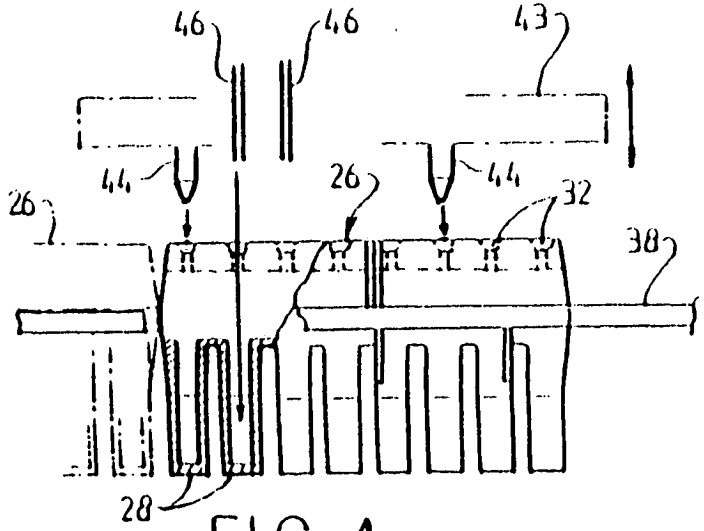

FIG. 4

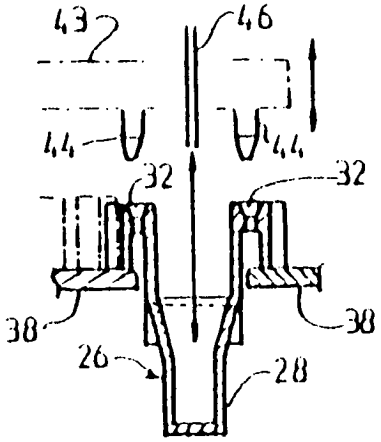

FIG. 5

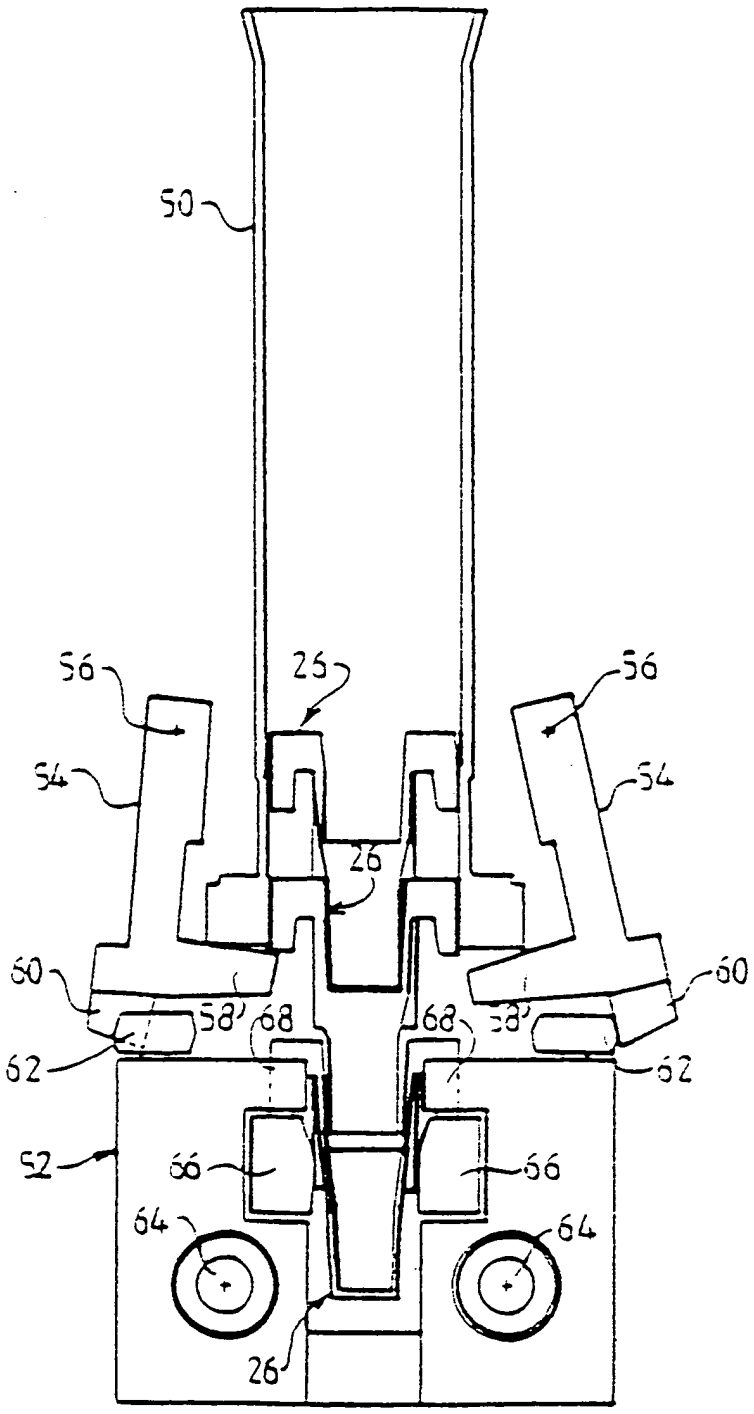

FIG. 6

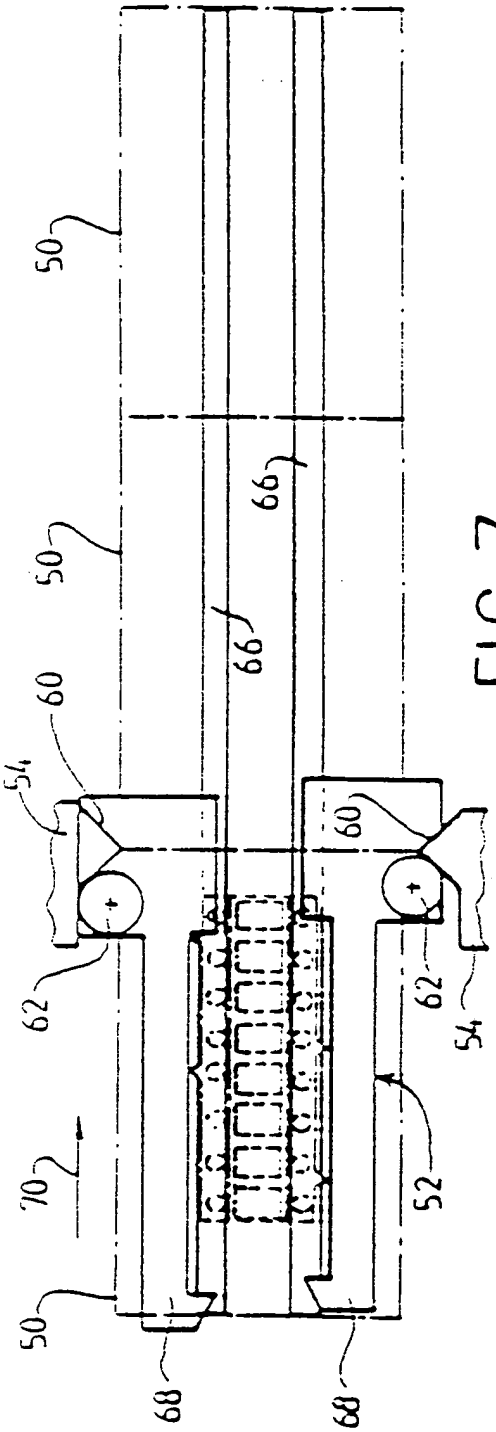
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FIG.7

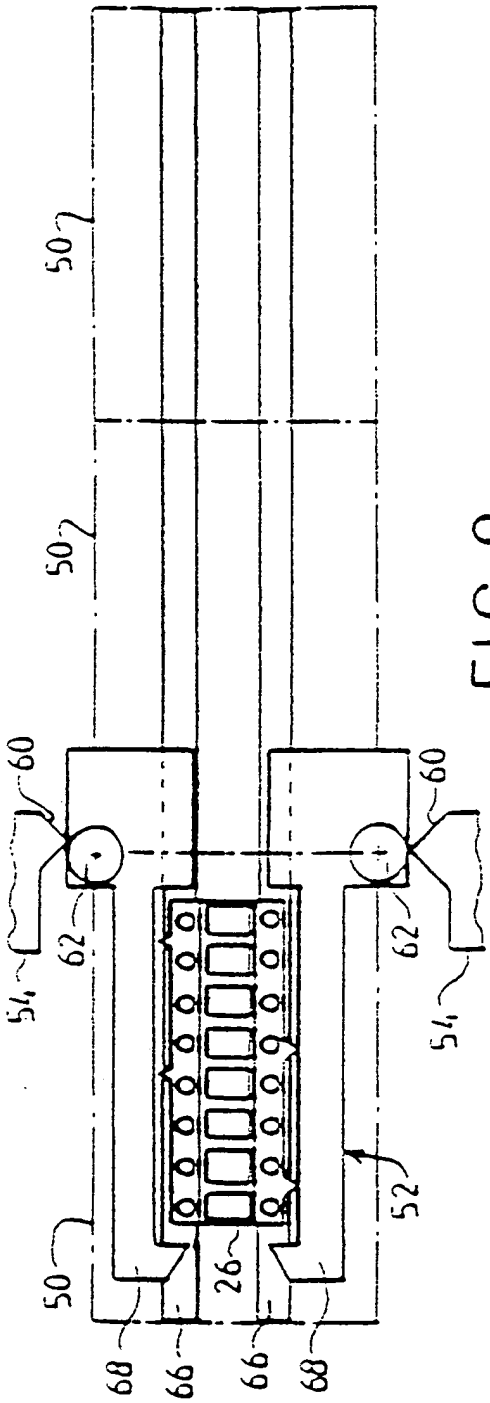
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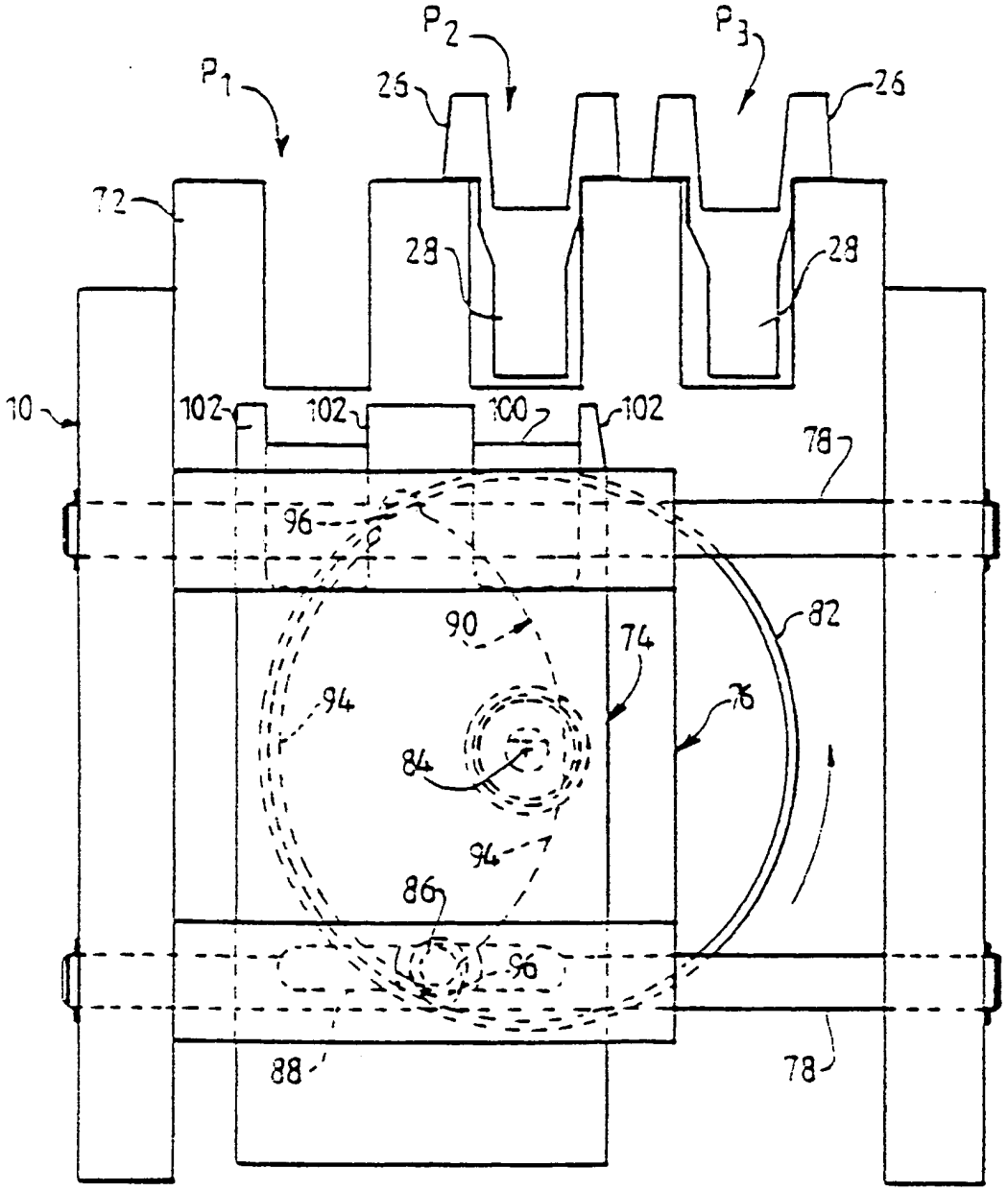
FIG.8


P1
P2
P3
26
26
72
28
28
10
102
102
100
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78
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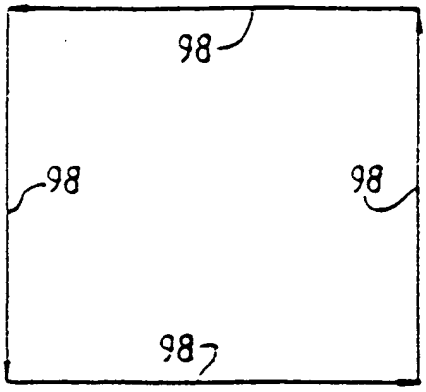
74
94
76
84
94
86
96
88
78

FIG.9


98
98
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98

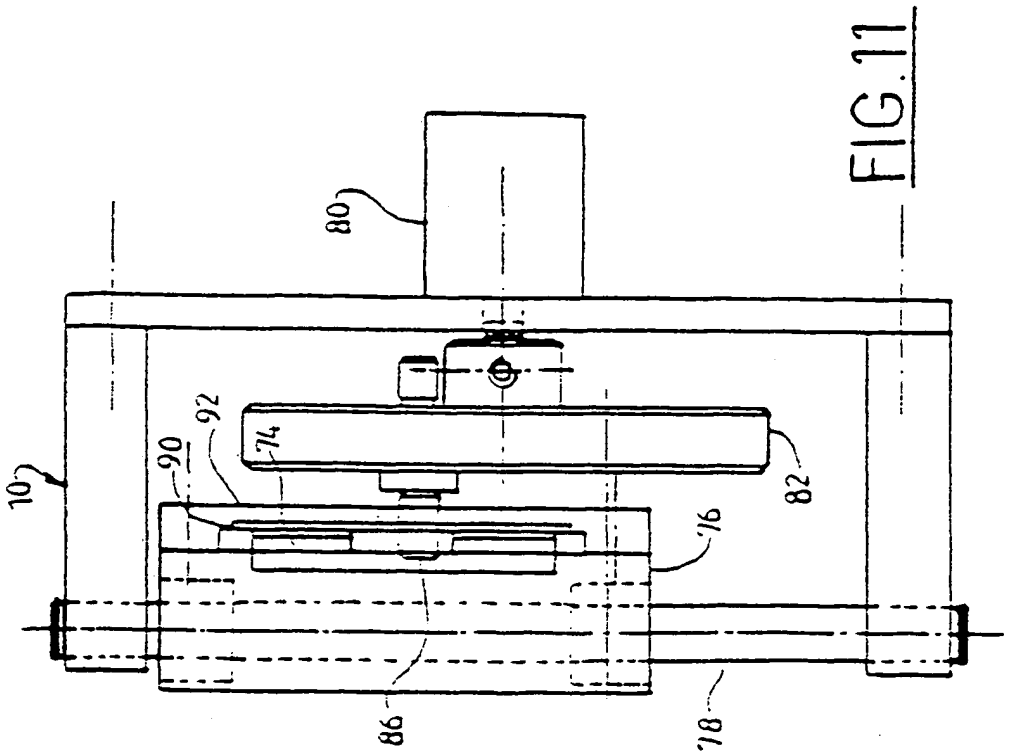


FIG.11

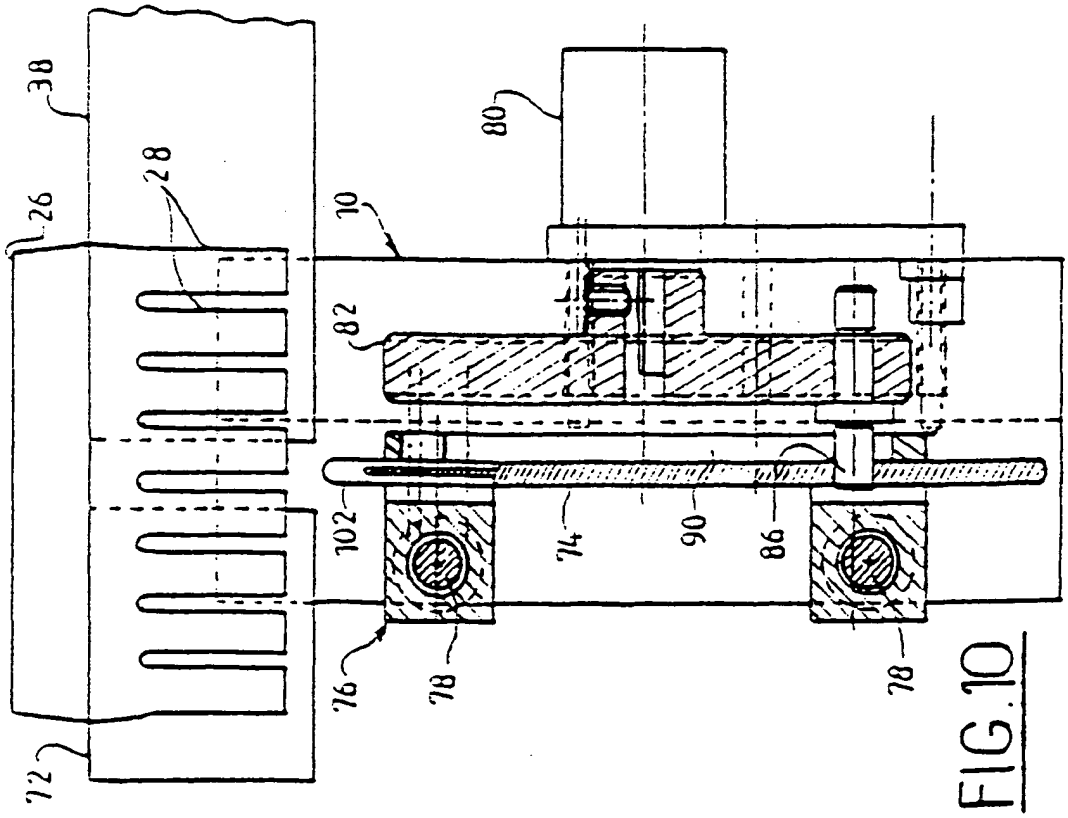


FIG.10

FIG.12

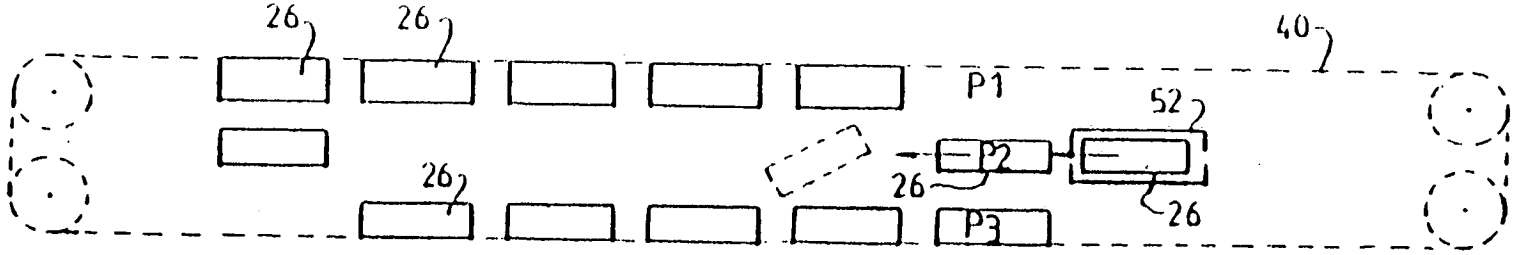


FIG.13

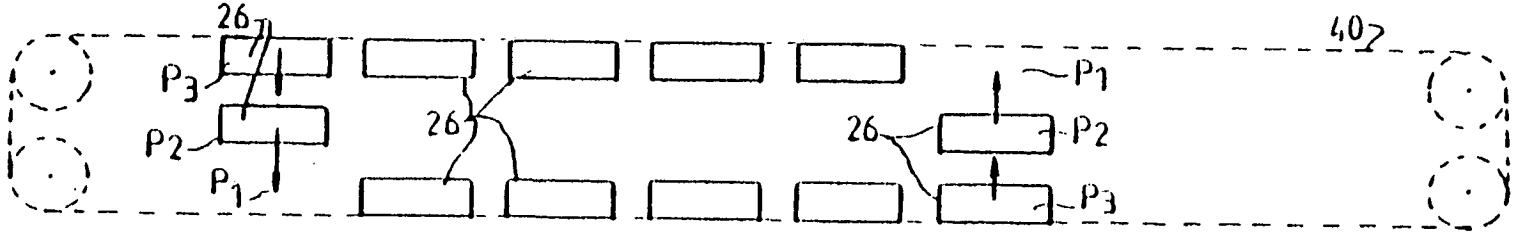


FIG.14

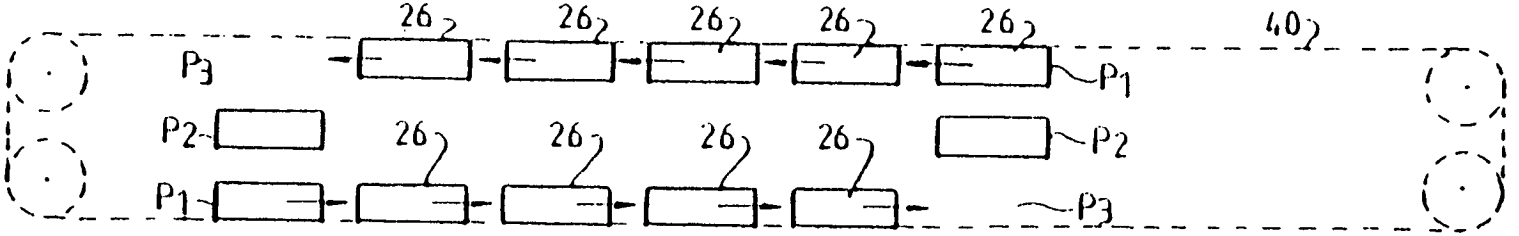
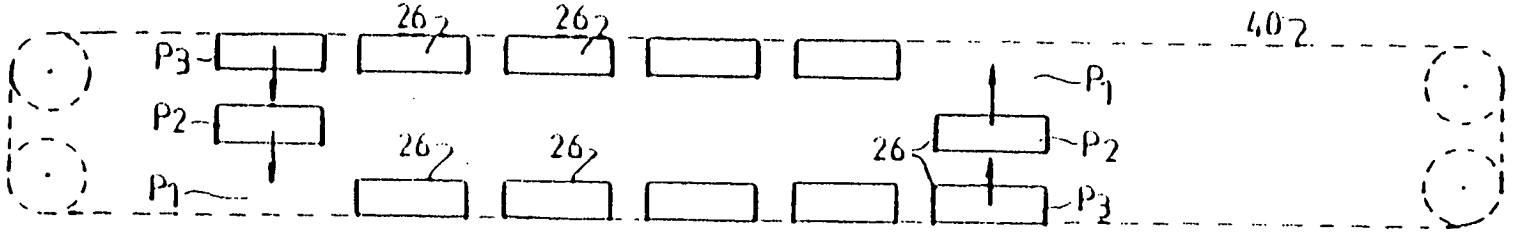


FIG.15



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